
Predictive factors for airway hyperresponsiveness in children with respiratory symptoms

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Background: Asthma diagnosis is a challenging condition, particularly in patients without obstructive pattern and reversibility on spirometry. Determination of airway hyperresponsiveness (AHR) may be helpful, but the procedure is time-consuming and not always practical.

Objective: To determine the potential factors that may predict the presence of AHR in children with asthmalike symptoms but without obstructive pattern and reversibility on spirometry.

Methods: All patients with asthmalike symptoms but without obstructive pattern and reversibility on spirometry were analyzed retrospectively between January 9, 2007, and December 30, 2009. The features of clinical history and laboratory results were analyzed with univariate and multivariate regression analysis.

Results: A total of 111 children between 6 and 18 years of age, with a median age of 10.2 years, were analyzed, and AHR was detected in 67 patients (60.3%). Multivariate logistic regression analysis revealed coexistence of nocturnal cough and exercise-induced cough (odds ratio [OR], 22.1; 95% confidence interval [CI], 3.1–159.2; $P = .004$), eosinophilia (OR, 18.7; 95% CI, 1.9–178.7; $P = .01$), and borderline bronchodilator response in forced expiratory volume in 1 second (between 7% and 11%) (OR, 10.1; 95% CI, 2.1–49.1; $P = .004$) as significant risk factors for the presence of AHR, whereas exercise-induced dyspnea was found to be related to the absence of AHR (OR, 0.2; 95% CI, 0.1–0.8; $P = .02$).

Conclusion: In children with asthmalike symptoms but with normal spirometry, certain features of clinical history and laboratory results can strongly predict the presence of AHR and may help less frequent use of challenge tests.

Ann Allergy Asthma Immunol. 2011;106:365–370.

INTRODUCTION

The diagnosis of bronchial asthma in children may be a challenging condition for clinicians in certain circumstances. The presence of some key signs and symptom indicators consistent with the characteristics of asthma may alert health care professionals; however, objective documentation of significant reversible airflow obstruction (increase in forced expiratory volume in 1 second [FEV₁] of ≥ 200 mL or $\geq 12\%$ from the baseline measure after inhalation of a short-acting bronchodilator) is usually required to determine a diagnosis of asthma.¹

Airway hyperreactivity to various stimulant agents is a characteristic feature of bronchial asthma. Determination of airway hyperresponsiveness (AHR) with methacholine challenge (MCC) is a safe, simple, standardized, and reproducible diagnostic tool used in clinical practice to establish the presence of asthma.² It has been widely used for many years in patients with pulmonary symptoms, and it is particularly

helpful in patients with asthmalike symptoms, such as cough, wheezing, and dyspnea, whose baseline spirometry values are normal and whose bronchodilator response is not significant enough to be diagnostic for bronchial asthma. The aim of this study was to determine the potential factors that could be predictive of the presence of AHR in children with asthmalike symptoms but without obstructive pattern and reversibility on spirometry.

METHODS

Study Participants

We retrospectively analyzed all children between 6 and 18 years of age who had undergone MCC at Hacettepe University Pediatric Allergy and Asthma Unit between January 9, 2007, and December 30, 2009. All children who were suspected of having asthma but without an obstructive pattern (baseline FEV₁ and/or FEV₁/forced vital capacity [FVC] ratio $< 80\%$ predicted) or significant ($\geq 12\%$) reversibility on spirometry were included.

Bronchial Provocation Tests

On the challenge day, patients were queried about prior use of drugs, and none had used short- or long-acting β -agonists, antihistamines, or inhaled oral corticosteroids/leukotriene receptor antagonists for at least 24 hours, 1 week, and 3 months

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Disclosures: Authors have nothing to disclose.

Received for publication December 2, 2010; Received in revised form January 19, 2011; Accepted for publication January 21, 2011.

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doi:10.1016/j.anai.2011.01.020

before the study, respectively. The children were challenged if they were capable of performing reproducible spirometry.

MCCs were performed according to a protocol described by Cockcroft et al³ as detailed previously.⁴ Briefly, after saline inhalation, doubling concentrations of methacholine were inhaled during a 2-minute tidal breathing period every 5 minutes, starting with 0.06 mg/mL up to 16 mg/mL or until a decrease in FEV₁ of at least 20% (PC₂₀) was obtained. The concentration of agents producing a PC₂₀ was calculated by linear interpolation on the log dose-response curve. A PC₂₀ of 8 mg/mL or less was considered to represent a positive test result. The aerosols were generated with a nebulizer (DeVilbiss model 646; DeVilbiss Co, Somerset, Pennsylvania) attached to an air compressor (Pulmo-Aid; DeVilbiss Co), with an output of 0.25 mL/min. The same nebulizer was used for each challenge. Duplicate spirometry was performed at 0.5 and 1.5 minutes after each inhalation. As suggested,⁵ methacholine was diluted in saline. Albuterol metered-dose inhaler was given to reverse bronchospasm. Spirometry was repeated 15 minutes after bronchodilator administration to verify reversal of the bronchospasm. Demographic data, symptom history, and spirometric findings of the patients were recorded.

Symptom Definitions

Symptoms were investigated according to questions provided from a standardized history sheet used in our outpatient clinic. *Wheezing* was defined as a positive response to the question, "Has your child had wheezing or whistling in the chest in the past 12 months?" *Daytime cough* was defined as a positive response to the question, "Has your child had daytime cough more than 2 days in a week and 1 week in a month in the past 12 months?" *Nocturnal cough* was defined as a positive response to the question, "Has your child been wakened at night due to a cough attack when she/he does not have a cold or chest infection at any time in the past 12 months?" *Exercise-induced cough* was defined as a positive response to the question, "Has your child ever seemed to cough more during or just after exercise compared to other children?" *Dyspnea* was defined as a positive response to the question, "Has your child ever had an attack of shortness of breath in the past 12 months?" *Exercise-induced dyspnea* was defined as a positive response to the question, "Has your child ever had an attack of shortness of breath following strenuous activity in the past 12 months?" Children with a positive answer to at least 1 of the questions were defined as having asthmalike symptoms.

Statistical Analysis

The SPSS software package version 15.0 (SPSS Inc, Chicago, Illinois) was used for all calculations. Group comparisons were established using Mann-Whitney tests for medians (and ranges) and the χ^2 test for categorical variables. $P < .05$ was considered significant. The strength of association among AHR, asthma, and comorbidities was expressed by odds ratio (ORs) and 95% confidence intervals (CIs).

The association between demographic, symptomatic, and spirometric parameters and AHR was analyzed using logistic regression modeling. Variables with $P < .20$ in univariate analysis were used for multivariate analysis. Major independent variables tested in univariate models were age, sex, family history of allergic diseases, tobacco smoke exposure at home, pet ownership, symptoms, atopy, accompanying atopic diseases, serum total IgE level, eosinophil percentage and absolute number, and baseline pulmonary function test data, including FVC, FEV₁, FEV₁/FVC ratio, response to bronchodilator, and methacholine PC₂₀ for FEV₁.

Parameters used in multivariate analysis were age, sex, nocturnal cough, exercise-induced dyspnea, coexistence of nocturnal cough and exercise-induced cough, IgE levels, serum eosinophilia (eosinophil counts ≥ 500 or $< 500/\mu\text{L}$), and borderline bronchodilator response in FEV₁ (ΔFEV_1 between 7% and 11%). Cutoff values representing the highest values for sensitivity and specificity were determined for eosinophilia and bronchodilator response in FEV₁ by constructing receiver operating characteristic curves. As for the nocturnal cough and exercise-induced cough, there was significance on univariate analysis but borderline insignificance on multivariate analysis; therefore, the analysis was repeated for the coexistence of nocturnal cough and exercise-induced cough.

RESULTS

A total of 111 MCCs were completed during the study period in children with a median age of 10.2 years (range, 6–18 years), and 53.2% of the patients were male. AHR was detected in 67 patients (60.3%). Demographic characteristics, admission symptoms, and laboratory parameters, including baseline spirometry values, classified by the presence or not of AHR are given in Table 1. The median age of patients with AHR was significantly younger than of those without AHR (9.9 vs 12.1 years; $P = .004$). Coexistence of nocturnal cough and exercise-induced cough was significantly more frequent in patients with AHR when compared with those without AHR (26.9% vs 6.8%; $P = .008$), whereas patient-reported dyspnea (20.9% vs 38.6%; $P = .04$) and exercise-induced dyspnea (26.9% vs 47.7%; $P = .02$) were more frequent in patients without AHR. Eosinophilia (eosinophil count $\geq 500/\mu\text{L}$) was determined in 23.4% of the patients with AHR and in 4.7% of those without AHR ($P = .009$). A borderline bronchodilator response (ΔFEV_1 between 7% and 11%) was significantly more frequent in patients with AHR when compared with patients without AHR (37.3% vs 9.3%; $P = .001$). When we combined our findings, the combination of coexistence of nocturnal cough and exercise-induced cough plus borderline bronchodilator response in FEV₁ was significantly more frequent in patients with AHR when compared with those without AHR (11.7% vs 0%; $P = .04$). Combination of eosinophilia and borderline bronchodilator response was also significantly more frequent in patients with AHR when compared with those without AHR (10.3% vs 0%; $P = .04$). However, the combination of eosinophilia (eosinophil count $\geq 500/\mu\text{L}$) plus coexistence of nocturnal cough and exercise-

Table 1. Comparison of Demographic Characteristics, Admission Symptoms, and Laboratory Findings of Patients According to Presence of AHR

	Study population (N = 111)	AHR positive (n = 67)	AHR negative (n = 44)
Demographic data			
No. (%) male	59 (53.2)	37 (55.2)	22 (50)
Age, median (IQR), y	10.2 (8.5–12.8)	9.9 (8.2–11.6)	12.1 (9.0–13.8) ^a
Family history of allergic disease, %	38.2	34.8	43.2
Skin test positivity, %	43.6	45.5	40.9
House dust mite	14.5	18.2	9.1
Pollen	36.4	37.9	34.1
Mold	1.8	1.5	2.3
Animal dander	4.5	4.5	4.5
Cockroach	1.8	0	4.5
Smoke exposure at home, %	28.3	25.4	32.5
Pet ownership, %	4.0	5.1	2.5
Accompanying allergic rhinitis, %	35.1	34.3	36.4
Accompanying eczema, %	1.8	1.5	2.3
Admission symptoms, %			
Daytime cough	73.0	76.1	68.2
Nocturnal cough	34.2	40.3	25.0
Wheezing	26.1	25.4	27.3
Dyspnea	27.9	20.9	38.6 ^a
Exercise-induced cough	30.6	34.3	25.0
Exercise-induced dyspnea	35.1	26.9	47.7 ^a
Coexistence of nocturnal cough and exercise-induced cough	18.9	26.9	6.8 ^a
Laboratory parameters			
Peripheral blood eosinophilia, median (IQR), %	2.7 (1.6–4.2)	2.7 (1.5–6.0)	2.5 (1.8–3.6)
Peripheral blood eosinophil count, median (IQR), / μ L	200 (100–340)	200 (100–400)	200 (100–300)
Patients with eosinophilia (eosinophil count >500/ μ L), %	15.9	23.4	4.7 ^a
Serum total IgE level, median (IQR), kU/L	87 (38.5–310)	106 (39–363)	77 (33.8–194)
Baseline FEV ₁ , median (IQR), %	97 (90–107.5)	96 (90–103.2)	98 (90–111)
Baseline FEV ₁ /FVC ratio, median (IQR), %	105 (99.5–111)	105 (96–109)	108 (103–112.3)
Patients with borderline bronchodilator response in FEV ₁ , %	25.5	37.3	9.3 ^b

Abbreviations: AHR, airway hyperresponsiveness; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

^a $P < .05$.

^b $P < .001$.

induced cough had slightly lost the significance. Table 2 lists the diagnostic values of our findings.

Multivariate logistic regression analysis revealed coexistence of nocturnal cough and exercise-induced cough (OR, 22.1; 95% CI, 3.1–159.2; $P = .004$), eosinophilia (OR, 18.7; 95% CI, 1.9–178.7; $P = .01$), and borderline bronchodilator response in FEV₁ (OR, 10.1; 95% CI, 2.1–49.1; $P = .004$) as significant risk factors for the presence of AHR, whereas exercise-induced dyspnea was found to be related to the absence of AHR (OR, 0.2; 95% CI, 0.1–0.8; $P = .02$) (Figure 1).

DISCUSSION

The results of the present study, conducted in a population of children suspected of having asthma and adolescents with normal or nondiagnostic results on spirometry, showed that coexistence of nocturnal cough and exercise-induced cough, peripheral blood eosinophilia, and borderline bronchodilator response in FEV₁ significantly predicted the presence of AHR, whereas patient-reported exercise-induced dyspnea was found to be a less reliable predictor.

Association of Symptoms With AHR

Results of several studies intended to determine the association between asthmalike symptoms and AHR have shown great variability. Chronic cough is one of the most common symptoms, and there are many differential diagnoses in childhood.⁶ In addition, AHR and development of asthma were found to be similar between coughing and noncoughing children.⁷ Nocturnal symptoms, due to overnight decreases in lung function, are known as common presentations of airway inflammation and AHR; in addition, nocturnal cough has even been reported in clinically stable asthmatic children.^{8,9} However, results of 2 population-based studies in both symptomatic and asymptomatic children did not establish an association between isolated nocturnal cough and AHR.^{10,11} Similarly, our results were also far from determining an association between AHR and isolated chronic daytime or nocturnal cough.

Exercise-induced wheezing and chronic cough have been reported as manifestations of AHR in children.¹² Strauch et

Table 2. Diagnostic Values of the Findings for Airway Hyperresponsiveness

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Coexistence of nocturnal cough and exercise-induced cough	26.9	93.2	85.7	45.5
Eosinophilia (eosinophil count $\geq 500/\mu\text{L}$)	23.4	95.3	88.2	45.5
Borderline bronchodilator response in FEV ₁	37.3	51.3	84.6	90.7
Coexistence of nocturnal cough and exercise-induced cough plus borderline bronchodilator response in FEV ₁	11.7	100	100	44.2
Eosinophilia (eosinophil count $\geq 500/\mu\text{L}$) plus borderline bronchodilator response in FEV ₁	10.3	100	100	44.1

Abbreviations: FEV₁, forced expiratory volume in 1 second; NPV, negative predictive value; PPV, positive predictive value.

al¹³ and Waked et al¹⁴ reported an association among wheezing, dyspnea, and AHR in a population study of 538 school-children and 134 adults, respectively. Wheezing was also found to be the most sensitive single symptom for asthma in the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA).¹⁵ However, our results failed to find an association between wheezing and AHR. The underlying reason may be that the term *wheezing* has no definite corresponding word in Turkish. Our data also showed that dyspnea, particularly exercise-induced dyspnea, was found to be more frequent in patients without AHR. In parallel to our findings, several studies^{16,17} have reported poor perception of dyspnea or exercise-induced dyspnea among children with AHR and asthma. Moreover, van Gent et al¹⁸ reported that perception of dyspnea was worse in children with undiagnosed asthma with AHR than in children with physician-diagnosed asthma. Hammo and Weinberger¹⁹ also speculated that the chest discomfort during vigorous exercise perceived as dyspnea was in fact associated with hypocapnia from hyperventilation without bronchospasm, and they concluded that children and adolescents had been misdiagnosed as having exercise-induced dyspnea.

Results of SAPALDIA concluded that respiratory symptoms obtained by medical history might be good predictors of asthma; however, the authors suggested the use of particular combinations of symptoms rather than a single symptom to determine more reliable predictors of AHR and asthma.¹⁵ Similarly, individual symptoms of nocturnal cough and exercise-induced cough were not predictive, whereas coexis-

tence of these 2 symptoms displayed the most significant association with AHR.

Association of Atopy and Eosinophilia With AHR

A number of studies in children, including birth cohorts, have reported an association between AHR and atopy.^{20–23} Moreover, early-onset atopy has been reported as a particularly strong risk factor for subsequent development of AHR.²⁴ Omenaas et al²⁵ and Obase et al²⁶ highlighted house dust mite sensitization as a significant predictor of increased AHR in a young adult community. However, in contrast to the findings of most studies, we observed no relationship among atopic status, high serum total IgE levels, and AHR. Although house dust mite sensitization was more frequent in children with AHR, the difference was far from approaching statistical significance. However, our study group is not a population-based group and consisted of highly selected patients, such as symptomatic children with normal baseline spirometry values and bronchodilator responses. Children with confirmed asthma diagnosis by objective documentation of reversible airflow obstruction were excluded. As a result, atopic sensitization may not have been found to be related to AHR.

Another finding of our study is that peripheral blood eosinophilia was associated with an increased risk of AHR in children with asthmalike symptoms. There are several studies in adult populations supporting our finding; however, pediatric data are limited. Ulrik²⁷ highlighted eosinophilia as a predictor of AHR. Sekerel et al²⁸ also determined this relationship in children and young adolescents. In addition, Gibson et al²⁹ concluded that airway eosinophils (sputum and nasal eosinophils) were linked to both asthma symptoms and AHR. Results of our analysis revealed a cutoff value of 500/ μL for peripheral blood eosinophilia.

Association of Spirometric Findings With AHR

Results of the European Community Respiratory Health Survey in Italy reported that baseline airway caliber measures, such as FEV₁ and FEV₁/FVC ratio, were negatively associated with AHR in young adults.³⁰ Several studies in adults and children with symptoms suggestive of asthma have also established a strong association between AHR and low functional status represented by decreased levels of FEV₁ and percentages of predicted FEV₁.^{31,32} A plausible explanation regarding functional findings that seem less important than

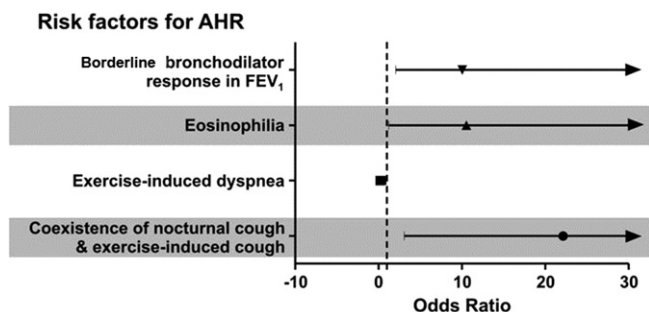


Figure 1. Risk factors for airway hyperresponsiveness.

the clinical symptoms to predict AHR might be the prior exclusion of patients with significant reversibility and low FEV₁. Contrary to these findings, baseline FEV₁ levels and percentages of predicted FEV₁ and FEV₁/FVC ratio were not found to be related to AHR in our study. On the other hand, similar to the work of Szeffler et al,³³ who established a 7.5% difference in FEV₁ as a parameter to determine a clinically meaningful response to asthma therapy, a borderline bronchodilator response (between 7% and 11%) in FEV₁ derived from baseline spirometry emerged as a novel predictor of AHR in our study. MCC is a time-consuming application that requires special facilities; therefore, performing MCC can be difficult even for secondary health care units dealing with asthmatic patients that perform baseline spirometry. Therefore, application of this parameter may be practical for clinicians who are not capable of performing MCC in daily practice.

Association of Asthma With AHR

Objective determination of AHR by bronchial provocation testing, particularly in atopic and symptomatic children, has been accepted as the "gold standard" for the diagnosis of asthma.^{1,3,34} Cockcroft³⁵ has concluded that a direct challenge with an agent such as methacholine has higher sensitivity with a high negative predictive value when compared with indirect challenges. Therefore, a negative result may reasonably exclude asthma diagnosis, whereas a positive challenge, particularly with a lower PC₂₀ value, may encourage physicians to perform a trial of asthma therapy. However, apart from bronchial asthma, AHR may be present in healthy children, allergic rhinitis patients, children with cystic fibrosis, or children with other chronic lung diseases of childhood.^{35,36}

Our study group consisted of patients who were referred to a tertiary asthma center due to diagnostic problems. Therefore, our results represent findings of a highly selected population, and as such they may not accurately match results of population-based studies. However, they are easily applicable to real life and can direct clinicians in daily practice when dealing with patients with symptoms suggestive of asthma. Our large sample size is another strength of our study.

In conclusion, coexistence of symptoms such as nocturnal cough and exercise-induced cough, borderline bronchodilator response in FEV₁, and peripheral eosinophilia may be predictors of AHR in children with asthmalike symptoms who have normal spirometric findings and lessen the need for MCC.

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